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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
02/26/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/779,746	GREER, SHELDON B.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,22-24,28-33 and 39-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,22-24,28-33 and 39-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 22-24, 28-33, and 39-59 are presented for examination

Applicants' amendment filed 12/10/2007 has been received and entered into the application. Accordingly, claims 22, 32, 40-41, 49, 52, 55, and 57-58 have been amended.

Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Response to Arguments

Applicant's arguments filed 12/10/2007 have been fully considered but they are not persuasive. Applicant submits the following arguments with respect to the 35 U.S.C. 102(b) rejection of claims 22-24, 28-29, 32, 39, 42-44, and 47 as being anticipated by Greer (WO 85/01871).

Firstly, Applicant refers to the Rule 1.132 Declaration of Dr. Sheldon Greer, filed February 26, 2007, wherein Dr. Greer asserts that those skilled in the art would not have believed that administration of CldC and tetrahydrouridine (H_4U) without a pre-treatment with PALA, FdC, 4-N-methyl FdC, or FdU, followed by radiation treatment would have been a successful method of tumor treatment. However, WO 85/01871 explicitly teaches a method of sensitizing neoplastic tissue to radiation comprising the administration of 5-chlorodeoxycytidine (5-CldC) co-administered with tetrahydrouridine (Abstract). According to one aspect of the invention, patients having tumors requiring radiation therapy are administered, preferably on a slow release

basis, 5-chloro-2'-deoxycytidine and/or 5-chloro 2'-halo-2'-deoxycytidine. The deoxycytidine compound is preferably administered with a deamination inhibitor, preferably tetrahydrouridine, for a period of time until amounts sufficient to sensitize tumor tissue to radiation are present in the tumor tissue (page 3, lines 4-14). The reference thus explicitly teaches administering a combination of 5-chloro-2'-deoxycytidine and tetrahydrouridine to a patient having a tumor about to undergo radiation therapy. In fact, Claims 1-4 of the WO document explicitly recite methods of sensitizing "susceptible neoplastic tissue" to radiation by administering the instantly claimed compounds. Although pretreatment with an inhibitor of pyrimidine biosynthesis (*e.g.*, the agents excluded from the methods instantly claimed) is also disclosed in the reference as an optional method, it is clear that Greer also unequivocally teaches administering a combination of 5-chloro-2'-deoxycytidine and tetrahydrouridine so as to sensitize tumors to radiation therapy (page 3, lines 4-14), thus anticipating the claimed methods.

Secondly, Applicant argues that it is an "unexpected finding" of the present application that CldC + H4U alone at higher doses could result in effective amounts of CldUMP and CldU in tumors without the need for modulation. While it may be true that this mechanism was not known before the filing of this application, the fact remains that WO 85/01871 explicitly teaches administering CldU + H4U prior to radiation as a radiation sensitizer. Further, WO 85/01871 teaches that when CldC is administered with H4U, CldC should be converted preferentially at the tumor site to CldUMP in human tumors possessing high levels of deoxycytidine kinase and dCMP deaminase (page 9, lines 16-28). WO 85/01871 goes no to provide a typical irradiation experiment involving i.p. injection of CldC + H4U every 8 to 10 hours in a 30 to 36 period (page 10, lines 4-6). Thus, while pretreatment with PALA, FdC, 4-N-methyl FdC, or FdU prior to

CldC + H4U may be a preferred embodiment of the invention of WO 85/01871, the fact remains that the reference teaches that CldC + H4U is useful to sensitize tumors to irradiation.

Accordingly, the Examiner is not persuaded that WO 85/01871 does not teach a method of sensitizing tumors to radiation comprising administering CldC + H4U. The rejection is maintained for the reasons of record and is reiterated below. With respect to the 35 U.S.C. 103 rejections set forth in the previous Office Action, the Examiner refers to the above discussion because Applicant only traverses these rejections with respect to the teachings of WO 85/01871.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-24, 28-31, 43-46, 49-51, and 55-56 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection necessitated by Applicant's amendments to claim 22.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition,

such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, claim 22 has been amended to recite the limitation wherein 5-chloro-2'-deoxycytidine and tetrahydrouridine are administered in amounts "effective to produce elevated levels of CldUMP and CldU" in a tumor. No support was found in the originally filed disclosure for such a limitation in the claims. While the specification indicates that CldUMP is "formed from CldC" (page 5, [0053]), there is no disclosure in the specification that 5-chloro-2'-deoxycytidine and tetrahydrouridine are administered in amounts that produce "elevated levels of CldUMP and CldU" in a tumor. The originally filed disclosure only provides support for administering 5-chloro-2'-deoxycytidine and tetrahydrouridine are administered in amounts that "sensitize" a tumor to radiation.

Accordingly, the amendment to claim 22 as introduced in Applicant's response filed 12/10/2007 introduces new matter into the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22-24, 28-29, 32, 39, 42-44 and 47 are again rejected under 35 U.S.C. § 102(b) as being anticipated by **Greer** (WO 85/01871; Published May 9, 1985).

Instant claim 22 recites a method of "achieving tumor control and improved irradiation efficacy" comprising two steps. First, a patient is administered CldC and tetrahydrouridine (H_4U) in amounts effective to produce elevated levels of CldUMP and CldU in a tumor. Second, the patient is exposed to an effective level of radiation delay the growth of said tumor.

Greer teaches a method of sensitizing neoplastic tissue to radiation comprising the administration of 5-chlorodeoxycytidine (5-CldC) co-administered with tetrahydrouridine (H_4U) (Abstract). Further, Greer teaches that when CldC is administered with H_4U, CldC should be converted preferentially at the tumor site to CldUMP in human tumors possessing high levels of deoxycytidine kinase and dCMP deaminase (page 9, lines 16-28). The reference thus explicitly teaches step one of the instant claims.

The invention of Greer provides therapeutic materials and procedures for treating solid tumors using X-ray or gamma ray, beta, neutron and other radiation sources (page 2, lines 10-

15). According to one aspect of the invention, patients having tumors requiring radiation therapy are administered, preferably on a slow release basis, 5-chloro-2'-deoxycytidine and/or 5-chloro 2'-halo-2'-deoxycytidine. The deoxycytidine compound is preferably administered with a deamination inhibitor, preferably tetrahydrouridine, for a period of time until amounts sufficient to sensitize tumor tissue to radiation are present in the tumor tissue (page 3, lines 4-14). The reference thus explicitly teaches administering a combination of 5-chloro-2'-deoxycytidine and tetrahydrouridine to a patient having a tumor about to undergo radiation therapy.

The slow release formulations of Greer anticipate the limitations of instant claim 24. Low concentrations of tetrahydrouridine are taught to protect the nucleoside analogs from systematic catabolism whereas with high concentrations of tetrahydrouridine, CldC "should be converted preferentially at the tumor site to CldUMP in human tumors possessing high levels of deoxycytidine kinase and dCMP deaminase (page 9, lines 20-28). Claims 1-4 of the WO document explicitly recite methods of sensitizing "susceptible neoplastic tissue" to radiation by administering the instantly claimed compounds. Although pretreatment with an inhibitor of pyrimidine biosynthesis (*e.g.*, the agents excluded from the methods instantly claimed) is also disclosed in the reference, it is clear that Greer also unequivocally teaches administering a combination of 5-chloro-2'-deoxycytidine and tetrahydrouridine so as to sensitize tumors to radiation therapy (page 3, lines 4-14). While such therapy may be *enhanced* by co-administration with an inhibitor of pyrimidine biosynthesis, the fact remains that 5-chloro-2'-deoxycytidine and tetrahydrouridine are alone effective to sensitize tumors to radiation when administered without such an inhibitor of pyrimidine biosynthesis.

The instantly claimed methods only require that a tumor be sensitized to radiation when a patient is administered 5-chloro-2'-deoxycytidine and tetrahydrouridine followed by an effective level of radiation. It is clear from the Greer reference that administration of 5-chloro-2'-deoxycytidine and tetrahydrouridine is effective to sensitize tumors to irradiation. As such, Greer clearly anticipates the claimed method of treating tumors comprising sensitizing tumors to radiation by administering 5-chloro-2'-deoxycytidine and tetrahydrouridine and exposing a patient to an effective level of radiation.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 30-31 and 40-41 are again rejected under 35 U.S.C. § 103(a) as being obvious over **Greer** (WO 85/01871; Published May 9, 1985) in view of **Shepherd *et al.*** (Cancer, 1992, vol. 70, pages 2250-2254, Abstract).

Greer teach as applied to claims 22-24, 28-29, 32, 39, 42-44 and 47, *supra*. Greer does not explicitly teach the use of yttrium-90 as a radiation source.

However, Shepherd *et al.* disclose that yttrium-90 microspheres have been used in the treatment of primary hepatocellular carcinoma (Abstract).

Thus, the instantly claimed methods wherein the radiation source comprises yttrium 90 needles would have been *prima facie* obvious in view of Shepherd *et al.* who teach that yttrium-90 is a radiation source used in the treatment of cancer. The skilled artisan would be imbued with at least a reasonable expectation that yttrium-90 would be a viable source of radiation in the

treatment methods of Greer. The motivation to use other radiation sources is clearly found in Greer, who teaches that radiation can be from "other radiation sources", aside from those explicitly disclosed (page 2, lines 10-15).

Claims 33, 45-46, 48, 50-51, 53-56 and 58-59 are rejected under 35 U.S.C. § 103(a) as being obvious over **Greer** (WO 85/01871; Published May 9, 1985).

Greer teach as applied to claims 22-24, 28-29, 32, 39, 42-44 and 47, *supra*. Greer does not explicitly teach the treatment of the specific tumors (*e.g.*, lung, prostate, breast, etc.) recited in the instant claims. The reference also does not explicitly teach the treatment of tumors resulting from gene silencing.

However, given the broad teachings of Greer as discussed *supra*, the skilled artisan would reasonably expect that the methods of sensitizing tumors to irradiation as taught in Greer could be predictably used to treat tumors of different organs. It is recognized in the art that radiation therapy is a useful, predictable treatment of tumors of different origin and etiology. As such, the skilled artisan could readily apply the methods of Greer to patients having tumors in different organs or arising from a different natural or environmental cause.

Claims 49, 52 and 57 are rejected under 35 U.S.C. § 103(a) as being obvious over **Greer** (WO 85/01871; Published May 9, 1985) in view of **Nagatake *et al***. (Cancer Research, 1996, vol. 56, pages 1886-1891).

Greer teach as applied to claims 22-24, 28-29, 32, 39, 42-44 and 47, *supra*. Greer does not teach the treatment of a tumor associated with hypermethylation.

However, Nagatake *et al.* disclose that hypermethylation of DNA is recognized as a consistent molecular change in human cancers, including lung cancer (page 1886, left column, first paragraph).

Thus, the instantly claimed methods of treating tumors associated with hypermethylation of nucleic acids would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Greer discloses a method of sensitizing neoplastic tissue to radiation comprising the administration of 5-chlorodeoxycytidine (5-CldC) co-administered with tetrahydrouridine (H_4U) (Abstract). Nakatake *et al.* disclose that altered DNA methylation may play a role in the oncogenesis of human neoplasms, including lung cancer. The skilled artisan would be imbued with at least a reasonable expectation that the methods disclosed in Greer could be used to treat tumors associated with hypermethylation of nucleic acids because the Greer reference is clearly not limited to the treatment of any particular tumor of specific etiology. Further, the skilled artisan could predictably use irradiation to treat any tumor regardless of etiology. Such methods of treating tumors with irradiation are commonplace in the art of treating cancer.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
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